

REMARKS

Status of the Claims

Claims 1-4, 9-14, 16, 28, 29, 43, and 45-50 are pending. Claims 46-50 were withdrawn from further consideration in response to a restriction requirement by the Examiner, under 37 C.F.R. §1.142(b).

In the present Response, claims 11-13, 16, and 47-49 are cancelled, without prejudice; claims 1-4, 9, 10, 14, 28, 29, 46, and 50 are amended; and new claims 51-62 are added. Thus, after entry of these amendments, claims 1-4, 9, 10, 14, 28, 29, 43, 45, 46, and 51-62 are presented for consideration.

Applicants note the withdrawal of the method claims in the previous action. Applicants, however, respectfully request that after the elected composition claims have been found to be allowable, all withdrawn process (methods) claims which depend from or otherwise include all of the limitations of the allowed product claims be rejoined. MPEP §821.04 (7th Ed., Revision 1, Feb. 2000); *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995); *In re Brouwer*, 37 USPQ2d 1663 (Fed. Cir. 1995); 1184 OG 86, 3/26/96. Therefore, because the method claims depend from the composition claims and would incorporate all the limitations thereof, Applicants respectfully request rejoinder after such time as the composition claims are deemed allowable.

Pursuant to the Office Action, claims 1-4, 9-14, 16, 28, 29, 43, and 45 are rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

Applicants respectfully submit that the claim amendments find support in the specification, in general. In particular, support for claims drawn to nucleic acids having at least 75, 80, 85, 90, 95, or 95% identity to SEQ ID NO:3 can be found, *inter alia*, at page 2, lines 4-8, of the specification. Support for claims drawn to nucleic acids that "selectively hybridize" can

be found, *inter alia*, at page 15, line 28, to page 16, line 10. Support for claims drawn to fragments can be found, *inter alia*, at page 2, line 31, to page 3, line 2; and page 68, line 31, to page 69, line 2. Support for claims drawn to nucleic acids of the invention flanked by heterologous sequences, such as expression vectors can be found, *inter alia*, at page 3, lines 3-7; and page 10, lines 21-30. Support for claims to nucleic acids of the invention in vectors can be found, *inter alia*, at page 3, lines 3-5. Support for claims to nucleic acids of the invention having labels can be found, *inter alia*, page 69, lines 10-19. Support for claims to nucleic acids of the invention in kits and arrays can be found, *inter alia*, at page 4, lines 16-24; and page 5, lines 1-4. Support for claims to methods for diagnosing GCA can be found, *inter alia*, page 5, lines 15-21. Applicants submit that no new matter has been introduced by the instant amendments.

Applicants' Invention

Applicants respectfully submit that they have discovered that SEQ ID NO:3 is found in GCA positive tissue and not in GCA negative tissue. According to one embodiment of the invention, Applicants have shown, in the previously filed declaration by Dr. Lynn Gordon, that nucleic acids can be used to detect SEQ ID NO:3, which can be used to diagnose GCA. The experiment conducted by Dr. Gordon is only one example of the compositions and methods of the invention.

Issues under 35 U.S.C. §112, first paragraph

Claims 1-4, 9-14, 16, 28, 29, 43, and 45 are rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree.

The Patent Office on page 3, lines 13-17, alleges that the specification discloses that the nucleic acid of SEQ ID NO:3 is a genomic DNA identified using a differential screen for sequences associated with GCA and that when the nucleic acid of SEQ ID NO:3 is expressed to

produce a fusion protein consisting of SEQ ID NO:4 and GST, the fusion protein is differentially bound by antisera from GCA patients.

Applicants submit that while SEQ ID NO:3 was discovered in a genomic library, that does not mean that SEQ ID NO:3 is a genomic DNA. For example, Applicants submit that another possible interpretation is that SEQ ID NO:3 is an exogenous nucleic acid from an invading bacterial or viral agent. The point of interest is that SEQ ID NO:3 is found in GCA positive tissue and not in GCA negative tissue. Applicants further submit that the experiments performed by Dr. Gordon and reported in the declaration proves that nucleic acids, *e.g.*, primers to SEQ ID NO:3, can be used to diagnose GCA. The declaration was submitted to show that nucleic acids of the invention had specific, substantial, and credible utility. Applicants thank the Patent Office for acknowledging utility of the invention and withdrawing that rejection.

The Patent Office cites the Guidelines for the Examination of Patent Applications Under 35 U.S.C. §112, first paragraph "Written Description" Requirement as stating that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of the relevant, identifying characteristics, *i.e.*, structure or other physical and or chemical properties, by function characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus.

Applicants, in turn, direct the Patent Office to its Revised Interim Written Description Guidelines Training Materials (hereinafter "Guidelines") which can be found on its website. Applicants have included Example 14 of the Guidelines, the section entitled "Product by Function," in the instant Response. In Example 14, a single disclosed species was sufficient to meet the written description requirement for claims drawn to variants of the disclosed species because all members of the genus had to meet a structural requirement and a functional requirement. Thus, the Patent Office, in its own Guidelines, finds the use of a single disclosed species sufficient to satisfy written description if the claims provide structural and functional

elements to distinguish between members that are encompassed by the claims and those that are not, in this case by percent sequence identity and function.

Moreover, Applicants include a copy of Trilateral Project 24.1, issued as a joint effort by the USPTO, EPO, and JPO. On page 4, question 2, a question was asked whether DNA characterized by "having some extent of identity to a DNA sequence" was allowed. The example of a claim directed to a DNA sequence encoding protein X, said DNA sequence having at least 40% identity to the DNA, is given. The response from all three offices is that the claim is clear if an appropriate definition of "identity" is provided in the specification. Applicants submit that an appropriate definition is provided at least at page 14, line 30, to page 15, line 27, of the specification. Moreover, page 15, question 6, dealing with claims to DNA with identity to a disclosed sequence, makes clear that the USPTO does not question "making" such products and only questions their use, which goes more to the question of an appropriate functional requirement. Again, it appears clear that a claim meets the requirements of 35 U.S.C. §112, first paragraph, written description, if it provides structure and function to the claimed subject matter so as to reasonably apprise one of ordinary skill in the art of the full scope of the claim.

On page 4 of the Trilateral project, question 3, a question was asked about the requirement for specifying a claim in which DNA is characterized by "hybridizing" to a specific DNA sequence encoding protein X. The USPTO stated that for purposes of clarity, there are no requirements for specifying the term "hybridizes," and the term "hybridizes" is itself a term of art which is clear though broad. On page 14, question 3, dealing with a claimed DNA characterized by the term "hybridize," the USPTO stated that the breadth of the claim includes more DNA embodiments than allelic mutants, and the necessary analysis requires an assessment of the adequacy of the description in the specification as to the identification of the biological activity of X. Yet again, the focus is on whether the scope of the claims can be determined by structure and function.

Applicants point to page 7, at the bottom, where the claimed invention is a DNA fragment used as a probe. The three offices state that a DNA fragment must be clearly defined by technical features. The USPTO explained that a probe claim relating to

addition/deletion/substitution would be very difficult to draft because encompassed within the claim are probes which may be specific for a region of the disclosed sequence that is varied. However, Applicants submit they have drafted the claims such that they meet the standards for patentability by providing structure and function to all members of the claimed genus so that one of ordinary skill in the art would comprehend the full scope of the claims.

Applicants' claims are directed to nucleic acids that have structure and function. For example, claim 1 is directed to nucleic acids that have at least 75% identity to SEQ ID NO:3 or its complement. One of ordinary skill in the art can readily determine if a nucleic acid is within the scope of the claims by comparing the nucleotide sequences.

In addition, claim 1 provides a physio-chemical property of the claimed nucleic acids in that they must selectively hybridize to SEQ ID NO:3 or its complement. "Selectively hybridize" refers to being able to detect SEQ ID NO:3 or its complement at least about 10 times above background. Moreover, the specification discloses information that was part of the knowledge of the skilled artisan at the time the application was filed about how to construct probes and primers, for example, at pages 20, lines 5-19; and page 21, line 27, to page 23, line 17 of the specification. Hybridization, for the skilled artisan, is a basic research tool. For example, a search of the term "hybridization" on the PubMed database retrieved 106,065 articles published at the time the instant application was filed. Accordingly, Applicants submit that hybridization, probes, and hybridization conditions were well known to the skilled artisan.

Finally, claim 1 also provides a function for the claimed nucleic acids, in that they must selectively hybridize to SEQ ID NO:3 or its complement, the utility of which has been addressed in a previous Response. Accordingly, Applicants respectfully submit that claim 1 is adequately described in the specification. Applicants further submit that for similar reasons, all pending and new claims are adequately described to one of ordinary skill in the art.

Applicants acknowledge the comment on page 5, lines 15-16, of the Office Action, that the instant rejection is set forth with respect to an alleged lack of written description and not an enablement rejection.

Applicants respectfully submit that as advised by the Patent Office at page 5, lines 27-28, of the Office Action, Applicants have limited the nucleic acids to nucleic acids with defined structures, thereby obviating the instant rejection.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of pending claims 1-4, 9 10, 14, 28, 43, 45, 46, and 51-62 based upon 35 U.S.C. §112, first paragraph, as well as allowance of the pending and new claims.

CONCLUSION

Applicants request that the Examiner reconsider the application and claims in light of the foregoing reasons and amendments and respectfully submit that the claims are in condition for allowance.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues and to work with the Examiner toward placing the application in condition for allowance.

Attached is a marked-up version of the changes being made by the current amendment.

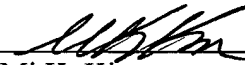
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Applicants believe that no additional fees are necessitated by the present Response. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2/11/2003



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Version with markings to show changes made

In the claims:

Claims 11-13, 16, and 47-49 have been cancelled, without prejudice.

Claims 1-4, 9, 10, 14, 28, 29, 46, and 50 have been amended as follows:

1. (4x Amended) An isolated or recombinant nucleic acid consisting of [comprising] a nucleic acid sequence having at least 75% sequence identity to [consisting essentially of] SEQ ID NO:3, or its complement, wherein the nucleic acid selectively hybridizes to SEQ ID NO:3 or its complement [nucleic acid is capable of identifying or detecting a Giant Cell Arteritis (GCA) associated nucleic acid].
2. (3x Amended) An isolated or recombinant nucleic acid fragment [The nucleic acid] of a nucleic acid of claim 1, 4, or 45, wherein the nucleic acid fragment [sequence] is 10 to 20 to 30 [50] nucleotides and selectively hybridizes to SEQ ID NO:3 or its complement.
3. (4x Amended) An isolated or recombinant nucleic acid fragment [The nucleic acid] of a nucleic acid of claim 1, 4, or 45, wherein the nucleic acid fragment [sequence] is [at least 50] 30 nucleotides or more and selectively hybridizes to SEQ ID NO:3 or its complement.
4. (4x Amended) An isolated or recombinant nucleic acid consisting of [comprising] a sequence as set forth in SEQ ID NO:3, or its complement.
9. (3x Amended) [A nucleic acid probe comprising] The nucleic acid of claim 1, 4, or 45, or fragments thereof that selective hybridize to SEQ ID NO:3, comprising a label [a nucleotide sequence consisting essentially of a sequence which specifically hybridizes to a nucleic acid comprising a sequence as set forth in SEQ ID NO:3 under stringent conditions, wherein the stringent conditions include a wash step comprising a wash in 0.2X SSC at a temperature of about 65°C for about 15 minutes].

10. (4x Amended) An isolated or recombinant nucleic acid fragment of claim 1, 4, or 45 [The nucleic acid of claim 1, claim 4, claim 9, or claim 45], wherein the nucleic acid fragment [sequence] is between about 15 and about 200 residues in length; is between about 25 and about 100 residues in length; or is between about 35 and about 75 residues in length.

14. (4x Amended) A transformed cell comprising the nucleic acid of claim 1, 4, or 45, or fragments thereof that selectively hybridize to SEQ ID NO:3 [claim 4, claim 9, or claim 45].

28. (4x Amended) A kit for detecting the presence of nucleic acid sequences associated with GCA in a sample comprising [a] at least one type of nucleic acid [as set forth in] of claim 1, 4, or 45 [claim 4, claim 9, claim 16, or claim 45], wherein the nucleic acid selectively hybridizes to SEQ ID NO:3 or its complement [of the sample detectably hybridizes to a nucleic acid as set forth in claim 1, claim 4, claim 9, claim 16, or claim 45 under in situ or in vitro conditions].

29. (4x Amended) A kit for detecting the presence of nucleic acid sequences associated with GCA in a sample comprising at least one type of [an amplification primer pair that can amplify a nucleic acid in the sample having a sequence as set forth in claim 1, claim 4, claim 9, claim 16, or claim 45 under in situ or in vitro conditions] nucleic acid fragment of claim 2.

46. (2x Amended) A method for detecting the presence of SEQ ID NO:3 for diagnosing GCA comprising the following steps:

- (a) providing a nucleic acid [as set forth in] of claim 1, 4, or 45, or fragments thereof that selectively hybridize to SEQ ID NO:3 [claim 4, claim 9, or claim 45, wherein the nucleic acid is capable of detectably hybridizing to a GCA associated nucleic acid under in situ or in vitro conditions];
- (b) providing a tissue sample comprising nucleic acids;
- (c) contacting the nucleic acid with the nucleic acids in the sample under hybridizing conditions; and

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(d) detecting whether the nucleic acid hybridizes to a nucleic acid in the sample, wherein the specific hybridization indicates the presence of SEQ ID NO:3 in the sample and is diagnostic for GCA.

50. (Amended) The method of claim [49] 62, wherein the amplification [amplication] is by polymerase chain [chaim] reaction (PCR).

Example 14: Product by Function

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of $A \longrightarrow B$. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of $A \longrightarrow B$.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

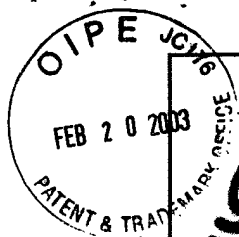
The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that

applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.



EPO

Trilateral

JPO

Web SiteUSPTO
USPTO

Trilateral Project 24.1
Biotechnology Comparative Study
on Biotechnology Patent Practices Comparative Study Report

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Foreword

In the beginning, the JPO notices that the JPO explains relevant provisions and practices mainly on the basis of 1994-Revised Patent Law (applicable to applications filed on and after 1995.7.1.)

1. Requirements for Disclosure and Claims General

The three Offices explain the reasons for rejection.

The USPTO explains, based on the Patent Act, Sections 101, 102, 103 and 112.

The EPO shows all the reasons, including the substantive requirements for disclosure and claims. On the other hand, the JPO explains in detail the requirements for disclosure and claims.

1.1 Claims

1.1.1 Clarity of Claims

1.1.1.1 General rules

(1) Is it allowed that a claim is defined only by the objective to be reached ?

If they can, how should such a claim be interpreted ?

Should such a claim be called a "single-means" claim ?

The three Offices point out that a claim defined only by the objective to be reached has problems in the light of clarity of claims and of enabling disclosure.

The USPTO states that a claim may not be defined only by the objective to be reached because it would not be commensurate in scope with the enabling disclosure.

The EPO states that the scope of a claim must be clearly and unambiguously defined and in general, claims which attempt to define the invention by a result to be achieved are not allowed, in particular if they only amount to claiming the underlying problem, in other words the result to be achieved, however, claims worded in terms of functional features may be allowed if the invention either can only be defined in such terms or cannot otherwise be defined more precisely without unduly restricting the scope of the claims and if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to the person skilled in the art and which do not require undue experimentation.

In the JPO, a patent application shall not be rejected on the ground of the lack of clarity of claims merely because a claim includes a statement defining a product only by the objective to be reached, however, it is the lack of clarity of claims, if a claimed invention cannot be clearly identified by a skilled person as a result of such claim statements, particularly, if the extent of the claimed invention is unclear to a skilled person even taking into account the specification, drawings and common general knowledge as of the filing.

(2) Is it allowed to use a result to be achieved as one of the elements (technical features)

of the claimed

invention in combination with the other elements (technical features) ?

Does the judgement depend on whether such an element is known to the public as of filing ?

Should such claim be called a "means-plus-function" claim ?

The three Offices allow to use a result to be achieved as one of the elements (technical features) of the claimed invention in combination with the other elements (technical features), however, the EPO allows such a claim only on the specific conditions as mentioned above 1.1.1.1(1) if such a element is the essential one.

(3) Is it allowed to refer to drawings or tables (including DNA sequence, amino acid sequence, cleavage map of the DNA, etc.) in the claims ?

The USPTO explains that a reference is allowed, as long as the meaning of the claims is definite. On the other hand, in the EPO, claims shall not, except where absolutely necessary, rely on the references to the description or drawings. An exceptional case is a claim for a DNA or protein; in these cases a reference to a drawing or table containing the DNA sequence, amino acid sequence or restriction map of the DNA, respectively, is allowed.

This handling is equal to that of the JPO on the basis of 1987-Revised Law, but the JPO explains that a reference is available when it leaves the claimed invention clear and concise under the 1994-Revised Law.

1.1.1.2 Details

1.1.1.2.1 Structural gene

(1) Where a claimed invention concerning structural gene is not characterized by its DNA sequence but

only by its function, is the claim specified clearly ?

ex. A DNA isolate consisting essentially of a DNA sequence encoding human protein X.

(Notes) The word "protein X" stands for a certain protein, like immune IFN, t-PA, etc. In the

following, the word "protein X" is used as the same meaning.

Is such a claim described above regarded as a "means-plus-function" claim or as a "single-means" claim?

The practices in the three Offices are common in that a claim directed to a structural gene characterized only by its function (encoding "protein X") is allowed provided the human "protein X" is clearly defined in the specification and is sufficiently characterized by structural features.

Concerning the terminology of "means-plus-function" and "single-means", the

USPTO states that such a claim is not normally labeled as a kind of "means" claim. The EPO mentions, in the prior questionnaire, such a terminology does not apply in the practice. The JPO explains that the claimed invention should be denied its novelty if any one of the every possible means for achieving the objective (result) stated in the claim is publicly known, and there is no distinction in the claim construction between so-called "single-means" and "means-plus-function" in this sense.

(2) Where a DNA is characterized by "having some extent of identity to a DNA sequence" in a claim, is

the claim specified clearly ?

ex. A DNA sequence encoding protein X, said DNA sequence having at least 40% identity to the DNA sequence in Fig. 1.

(Notes) Suppose that a specific DNA/amino acid sequence is described in "Fig. 1". In the following,

"Fig. 1" is used as the same meaning.

The three Offices, in principle, agree that it is clear if an appropriate definition of "identity" (homology) is provided in the specification, however, the EPO states that the limit of "at least 40% identity to the DNA sequence in Fig. 1" is too low to ensure that the protein encoded by the degenerated DNA sequences remains the same and the JPO states that enablement requirement should be examined because the claimed DNA having identity (homology) with the specific DNA may be unlikely to have similar activity as the specific DNA.

(3) What are the requirements for specifying a claim in which a DNA is characterized by "hybridizing" to a specific DNA sequence ?

For example, i) a DNA sequence has to be a naturally-occurring product, ii) the condition of hybridization must be defined, iii) the source of a DNA must be specified (ex. human being, mouse etc.)

ex. A DNA sequence encoding human protein X, said DNA sequence being selected from the groups consisting of:

- a) the DNA sequence set out in Fig. 1 or its complementary strand; and
- b) naturally obtainable DNA sequence which hybridizes under stringent conditions to the DNA sequence defined in a).

There are some differences in the answers of the three Offices.

In the USPTO, for the purposes of clarity, there are no requirements for specifying the term "hybridizes", and the term "hybridizes" is itself a term of art which is clear though broad.

The EPO answers that it is possible in a claim to characterize a DNA sequence by "hybridizing" to a specific DNA sequence only on condition that the hybridization

conditions are defined in the claim.

The JPO states that a hybridization claim can be defined by a description containing all the elements listed below as 1) - 3);

- 1) one or more nucleotide sequences defined in, for example, working example
- 2) the phrase of "under stringent conditions" in the claim (the conditions be provided in the detailed description of the invention)
- 3) property or function of encoded protein

(4) What are the requirements for specifying a claim like the following example ?

ex. A DNA encoding a protein which has the function of protein X and which comprises a derivative, by way of amino acid substitution, deletion, addition or insertion of the amino acid sequence set out in Fig.1.

For example, is it necessary to define the number of bases which may be added, deleted or substituted ?

The USPTO answers that definition of the terms substitution, deletion, addition and insertion do not require numerical definition for the purposes of clarity and specificity. However, the USPTO points out that the broadest interpretation of these terms would result in a very broad claim encompassing many DNAs. Moreover, proteins have many functions and the intended function of protein X is not recited possibly making the DNA indefinite.

In contrast, the EPO and the JPO state that an addition/deletion/substitution type claim can be defined with elements 1) - 3);

- 1) one or more nucleotide sequences or amino acid sequences defined in, for example, working example
- 2) a clear definition of the term "addition, deletion, substitution," provided that "the sequences added, deleted or substituted" have a high degree of identity (homology) with the sequences of 1)
- 3) property or function of encoded protein

(5) Allelic mutant, Derivative, Equivalent, Variant Where a claim states as an "allele or allelic mutant", or a "derivative", or an "equivalent", or a "variant" of a specific DNA sequence, is the claim specified early ?

ex. A DNA sequence encoding human protein X of the amino acid sequence depicted in Fig. 1 hereof or

allele or derivative thereof having the function of human protein X.

Again, there are some difference the practices in the two Offices (the EPO and the JPO) and these in the USPTO.

In the JPO, it depends on the definition of the terms in a specification whether or not the claim containing the above-mentioned terms is clear. To be judged clear, it is necessary to provide a clear description that the differences between the amino acid sequences of allele or derivative and the standard sequence shown in Fig. 1 are within a certain range.

The EPO states that on condition that a DNA sequence is clearly defined in a claim, the

variants etc. of the DNA sequence fulfill the requirements of clarity provided that the variants etc. of said DNA sequence are additionally all defined as encoding proteins which have the same properties as protein X.

On the other hand, the USPTO states that "derivative", "equivalent" and "variant" do not have well recognized, specific meaning in the art of molecular biology and their use as in this question would raise an issue as to specificity. The USPTO states that one would look to the specification and the state of the art to determine the definition of allele or allelic mutant.

1.1.1.2.2 Recombinant protein : Protein as obtained by using recombinant DNA technology

Where claims related to recombinant proteins are described in the same form as the claims of structural genes discussed in 1.1.1.2.1(1) - (5) above, would they be regarded in the same way ? If different judgement is made about those proteins, please discuss in this paragraph.

(1) In case where its amino acid sequence is not described and only its function is described in a claim.

ex. A recombinant protein having the function of human protein X.

(2) In case where a protein is described as "having some extent of identity" to a specific sequence in a claim.

ex. A protein having protein X function and which is encoded by a DNA, said DNA having at least 40% identity to the DNA sequence in Fig. 1.

(3) In case where a protein is characterized by "hybridizing" to a specific sequence.

ex. A protein having protein X function and which is encoded by a DNA sequence, said DNA sequence being selected from the groups consisting of:

a) the DNA sequence set out in Fig. 1 ;and

b) naturally obtainable DNA sequence which hybridizes under stringent conditions to the DNA sequence defined in a).

(4) In case where a protein is characterized by "addition-deletion-substitution".

ex. A protein having protein X function and which comprises a derivative, by way of amino acid deletion, substitution, insertion, inversion or addition of the amino acid sequence as encoded by the DNA in Fig. 1.

(5) Allelic mutant, Derivative, Equivalent, Variant

ex. Protein X of the amino acid sequence depicted in Fig. 1 hereof or allele or derivative thereof having the function of protein X.

These questions (1) - (5) correspond to the prior questions 1.1.1.2.1(1) - (5).

Concerning (1), the USPTO and the EPO comment that a recombinant protein being defined only by having the function of a certain protein X would lack clarity because a protein has several different functions.

As to (2) - (5), the answers of the two Offices (the EPO and the JPO) are the same as their answers of corresponding questionnaire 1.1.1.2.1(2) - (5); the USPTO gives answers that differ from their answer to the corresponding question 1.1.1.2.2(2), (3) and (5). The differences arise from the recitation of a protein function in the protein claims which is not present in DNA claims 1.1.1.2.1(2) and (3). The USPTO points out that the specification must be consulted to determine the meaning and clarity. The USPTO supplements its explanation for 1.1.1.2.1(2) by pointing out that it is often possible to arrive at different extents of sequence identity between sequences because of many different algorithms for comparing and many different variables in these algorithms.

Is there any difference to define claims between recombinant DNAs and recombinant proteins, in case that structural genes which encode proteins with a biological function are cloned ? If there are some differences, what is the reason for the differences ? For example, is the claim "a DNA encoding a protein X and which comprises a derivative by way of amino acid substitution, deletion, addition or insertion of the amino acid sequence set out in Fig. 1" definite ?

On the contrary, is the claim "a protein which has the function of protein X and which comprises a derivative by way of amino acid substitution, deletion, addition or insertion of amino acid sequence set out in Fig. 1" indefinite ?

If it is indefinite, does it become definite by describing "the function of protein X" more clearly and concretely ?

The EPO and the JPO reply that there are no differences between them.

The USPTO answers that such a claim as "a protein which has the function of protein X and which comprises a derivative ... in Fig. 1" is not clear, because a protein rarely has only one function. However, it may become clear, if the function of protein X is defined precisely.

1.1.1.2.3 DNAs, other than structural gene

(1) Where a claimed invention is directed to a DNA fragment used as a probe for analysis, are those forms of claims described in 1.1.1.2.1(2) - (4) above allowed ? If there are any more suitable words to define DNA fragments, please discuss them in this paragraph.

The three Offices agree, in principle, that a DNA fragment must be clearly defined by technical features, but there are some differences in their answers.

The USPTO explains that a probe claim relating to addition/deletion/substitution would be very difficult to draft because encompassed within the claim are probes which may be specific for a region of the disclosed sequence that is varied.

The EPO emphasizes a precise definition of the fragment/probe length or of the part of the amino acid sequence of the protein or peptide.

The JPO shows the two requirements for being a DNA probe for analysis; 1) it can strictly hybridize with polynucleotides to be detected, 2) it does not hybridize with polynucleotides concerning similar polypeptide, and as a result, enablement requirement is generally considered not to be satisfied in many cases where DNA probes for analysis are specified by homological, hybridization and addition/deletion/substitution sequences.

(2) Where a claimed invention is directed to a regulatory sequence like promoters and so on, are those forms of claims described in 1.1.1.2.1(2) - (4) above allowed ? If there are any more suitable words to define regulatory sequences, please discuss them in this paragraph.

Again, the three Offices coincide that a regulatory sequence must be clearly defined by technical features.

In particular, the USPTO and the EPO explain the requirements for such a claim, that is, mainly certain extent of identity, hybridization conditions and/or the kind and extent of mutations of the specific DNA sequence.

The JPO shows that the length of a nucleotide sequence corresponding to actual regulatory function in sequence confirmed to possess some regulatory function is extremely shorter than that of structural genes, therefore, it is likely that a DNA defined by identity (homology), hybridization, or addition/deletion/substitution relating to a regulatory sequence would lose the function of the original sequence.

1.1.1.2.4 Transformant, Fused cell

(1) Where the word "transformant" implies not only cell cultures and microorganisms but also plants and animals themselves, is a claim using the word "transformant" specified clearly ?

ex. The claim is, "A transformant transformed with a DNA sequence encoding for protein X.", and in the description of the invention defines "transformant" to include cell cultures, microorganisms, animals themselves and plants themselves.

The three Offices agree that the term "transformant" itself is not unclear.

In addition, the USPTO and the EPO point out that "transformant" may not be acceptable if the definition in the specification would be considered repugnant to the normally accepted usage of the term. Furthermore, the two Offices notice that a broad interpretation to include humans would be unacceptable.

(2) Where the claimed invention is directed to a fused cell which produces a monoclonal antibody, what is the element necessary in the claim other than the monoclonal antibody itself ? (ex. name of the used host cell or parental cell etc.)

The USPTO answers that it may be specified with a deposit designation.

Concerning the specific hybridoma, the similar answer is revealed by the EPO and the JPO. The two Offices, though, explain that a broad claim directed to a fused cell can be characterized by a combination of parent cells, function/properties and production (produced monoclonal antibody). And the USPTO concurs with the EPO and the JPO for such a broad claim.

1.1.2 Relationship between Claims and Description of the Invention **[ex.**

Support in description of the invention (Relationship between working examples and claims), Adequate written Description, etc.]

Please discuss those issues mentioned below in "1.2.1 Enablement Requirement" in this paragraph, if the USPTO or the EPO finds it more proper to handle those issues as a matter of "support" or "adequate written description" for the invention described in the claims.

(For example, if those issues mentioned below are considered under EPC Article 84 rather than EPC Article 83, it might be reasonable to handle them in this paragraph.)

The different thinking around this question is recognized between the EPO and the JPO.

In the JPO, it is enough to satisfy a requirement for the Patent Law Section 36(6)(i) that the matter corresponding to what is claimed is formally written in the detailed description of the invention. Consequently, it is usually discussed as the matter of "enablement requirement."

On the other hand, the EPO explains that an objection of lack of support under Article 84 EPC can often also be considered as an objection of insufficient disclosure under Article 83 EPC.

The USPTO gives answers that the specification must provide both a written description of the invention and sufficient enablement to practice the invention as claimed. These are separate and distinct requirements of the statute 35 U.S.C.112, first paragraph.

1.2 Description of the invention

1.2.1 Enablement Requirement (Adequacy of Disclosure)

1.2.1.1 General rules

The report "Consolidated Comparative Study of Patent Practices in the Field of Biotechnology Related Mainly to Microbiological Inventions"(1990.1) of Project 12.3 and the report "Comparative Study Report on Requirements for Disclosure and Claims"(1990) of Project 12.6 have been made. Considering these reports, please explain the following items.

(1) Please explain the examining practice related to "Enablement Requirement (Adequacy of Disclosure)" in detail.

For example, please refer to "how to make" and "how to use".

The three Offices coincide that enough or sufficient information is needed to carry out the claimed invention by a person skilled in the art, without undue experimentation and using his common general knowledge as of the filing.

In addition, the EPO states that the description must disclose any feature essential for carrying out the invention in sufficient detail to render it obvious to the skilled person how to put the invention into practice. Also, the JPO explains that normally one or more representative embodiments or working examples are necessary in the case of inventions in technical fields where it is generally difficult to infer how to make and use a product on the basis of its structure.

(2) Is there difference in the definition (level) of the "person skilled in the art" between the assessing inventive step and the assessing sufficiency of description ?

The three Offices show that there may be no practical difference about the term "person skilled in the art" itself, between the assessing inventive step and the assessing sufficiency of description.

The three Offices agree that the range of knowledge is limited only to the "common general knowledge" as of the filing, not to all the "state of the art" as of the filing including common general knowledge for assessing sufficiency of description.

(3) In determining whether claimed invention not accompanied by sufficient description in the specification can be carried out by a person skilled in the art, should an examiner take into consideration either the common general knowledge (such as well-known or commonly used art) or all the relevant documents in the state of the art ?

In general, an examiner should take into consideration the "common general knowledge" in all the three Offices.

The EPO notices that patent specifications may exceptionally be considered as forming part of common general knowledge in a field of, for example, biotechnology, which field is so new that the relevant technical knowledge is not yet available from textbooks.

(4) If the applicant presents the written argument (or the certificate on the result of experiment) which includes the explanation of how to make and how to use without amending the specification, may the reason for rejection related to the enablement requirement be overcome? Is it possible to take into consideration those relevant documents which were published after the filing date?

The three Offices give the same answer to this question, that is, the reasons for rejection related to the enablement requirement shall be overcome if the examiner determines that the claimed invention can be carried out by a person skilled in the art based on what is described in the specification and common general knowledge as of the filing, when the applicant presents literature that is clearly establishing the common general knowledge as of the filing in a written argument. The literature published after the filing may be also available if the contents of this literature clearly represent the common general knowledge as of the filing.

(5) What kind of factors may be taken into account in determining whether the experimentation required is undue (or unreasonable)?

The USPTO and the JPO point out the same several factors listed below;

- quantity of experimentation needed
- amount of direction or guidance given in the specification
- the presence or absence of working examples (shown only by the USPTO)
- the nature of the invention
- state of the prior art
- relative skill levels present in the technical area
- predictability of that particular art
- the breadth of the claims

The EPO explains that the sufficiency requirement would not be fulfilled if the successful performance of the invention is dependent on chance and is achieved in a totally unreliable way; however if repeated success is assured even though accompanied by a proportion of failures, this would not be considered as undue experimentation.

(6) Which one has the burden of giving reasons why the specification is (not) enabling, an examiner or an applicant?

The practices of the three Offices are common in that the initial burden of pointing out the reason of rejection is on the examiner. However, though the JPO and the EPO find that the burden of proof (the burden of persuasion) is finally on the applicant

throughout prosecution, the USPTO must always shoulder the burden of proving that the specification is not enabled.

(7) Where there are well-founded reasons to believe that a skilled person would not be able to extend teaching of the description to the whole of the field claimed, what kind of evidences should an examiner prepare necessarily ?

Should such reasons be supported by a published document ?

Please explain other examination practices related to "well-founded reasons" in detail, if any.

The USPTO explains that unpredictability in the art and lack of working examples are important in questioning whether the invention is enabled throughout the scope of the claim.

The EPO gives two examples that 1) a specific microorganism isolated by chance and not deposited is being claimed or 2) common general knowledge suggests a claimed invention would not be repeatable.

According to the answer of the JPO, among the concrete reasons is the reasoning that a skilled person would be unable to extend the particular enabling description in the detailed description of the invention to the whole of the field within the extent (or the metes and bounds) of the claimed invention.

Furthermore, the three Offices mention that the reasons of rejection should preferably be supported by reference documents.

(8) Where there was no variant of means to solve the problems in a claim other than the only one means used in the working example as of filing, should functional expression be accepted taking into account the other later developed means to achieve the same effect ?

The answers of the EPO and the JPO to this question are similar to the question 1.1.1.1 (1).

In particular, the JPO states that, with respect to an application having a claim defined by a result to be achieved and a disclosure of only one specific means to achieve the result, the enablement requirement is judged regardless of the existence or absence of other later developed means.

On the other hand, the EPO points out that a claim may be allowed covering all means later developed if the invention is major one opening up a new field and the teaching of the invention leads the later development.

Also, the JPO shows that inventive step of the claimed invention which defines a product solely by a result to be achieved should be denied when the result to be

achieved is a well-known technical problem and a certain product to be defined by the result is either known to or easy-to-invent to a person skilled in the art as of the filing, unless otherwise inventive step can be positively inferred by other facts, even if a specific means to solve the technical problem is not known as of the filing.

The USPTO states that such claims reciting means plus function are authorized, if the claim is drawn to a combination of elements.

1.2.1.2 Details

(1) The claimed invention is

- (a) a recombinant vector,**
- (b) a process for producing a recombinant vector,**
- (c) a transformant,**
- (d) a process for producing a transformant,**
- (e) a process for producing a recombinant protein X, or,**
- (f) a recombinant protein X.**

In the description of the invention, there is a working example of cloning cDNA encoding protein X, but there is no working examples of these inventions themselves.

In this case, does this claimed invention (a) - (f) mentioned above meet the enablement requirement respectively ?

The USPTO suggests that it is difficult for the USPTO to definitively determine enablement for the proposed working example and provide specific answers to the questions exemplifying (a) - (f), however, if the description is reasonably adequate to allow one skilled in the art to produce the protein via use of the cDNA as indicated, (a) - (f) would be enabled.

The EPO points out that claims to the subject-matter of (a) - (f) would appear to be enabled, supposing that the actual invention of the application is to be seen in the cloning of the cDNA is sufficiently disclosed in the application.

The JPO notices that in case where a person skilled in the art needs undue experimentation in order to express the structural gene and to make the corresponding protein without loss of the original activity as a mature product and the claimed invention which have no corresponding working example would not meet the enablement requirement.

(2) In the description of the invention, there is a working example of producing only one kind of transformant (ex. E. coli).

Where a claimed invention contains any other kind of transformants than E. coli, does this claimed invention meet the enablement requirement ?

And if this claimed transformant obviously contains an animal or a plant, does this claimed invention meet the enablement requirement ?

The three Offices agree that the answer to this question depends on the case.

As to an animal or a plant, the USPTO and the JPO point out there may be a well-founded reason that transformants in hosts other than the host used in the working example is non-enabling. On the other hand, the EPO states the same criteria as that of microorganism would apply in the case of animals or plants.

(3) The claimed DNA is characterized by the term "hybridize" (ex. A DNA sequence hybridizing to the DNA sequence X and encoding a polypeptide having the biological activity x).

Where the original cDNA sequence (the DNA sequence X) is disclosed in the description of the invention, while there is no working examples how to clone allelic mutants by way of hybridization, does this claimed invention meet the enablement requirement ?

If the claim contains not only natural-occurring but also artificial DNA, does this claimed invention meet the enablement requirement ?

The USPTO's answer seems to be different from those of the other two Offices.

According to the USPTO's answer, the breadth of the claim in the example does include more DNA embodiments than allelic mutants, and the necessary analysis requires an assessment of the adequacy of the description in the specification as to the means of identification of "biological activity X".

On the other hand, the other two Offices reply affirmatively, since it is within common general knowledge to clone other similar DNAs by way of hybridization (the EPO), or the hybridization technology was developed some 20 years ago and it has been used in the relevant field of technology since 1980 as a common method in order to obtain allelic mutants (the JPO).

As to artificial DNA, though, there seems to be different opinions between the EPO and the JPO; the EPO thinks there is no difference whether the DNA is natural or artificial. On the other hand, the JPO thinks many types of artificial DNA sequences, having low identity (homology), are possible to hybridize to the DNA sequence X even under stringent condition.

(4) The claimed DNA is characterized by the term "substitution, deletion, addition or insertion" (ex. A DNA sequence produced by way of nucleotide substitution, deletion, addition or insertion of the DNA sequence X).

Where the original DNA sequence (the DNA sequence X) is disclosed in the description

of the invention, while there is no working examples how to produce derivatives by way of substitution, deletion, addition or insertion of nucleotides, does this claimed invention meet the enablement requirement ?

Where the claimed sequence is very short (ex. A DNA sequence coding for the epitope of antigen), does this claimed invention meet the enablement requirement ?

The USPTO suggests that a description may be adequate if the description contains adequate guidance as to what compounds are envisioned and how to make such compounds.

The EPO replies that it is within ordinary skill in the art to obtain DNA sequences which are distinguished from a given DNA sequence X by way of substitution, deletion, addition etc.; and this would also apply to very short DNA.

The first half of the answer given by the JPO is similar to that of the EPO; the enablement requirement is generally satisfied without concrete disclosure such as a working example, provided that the application is filed after common technical knowledge was established with regard to the method of making an addition, deletion and substitution to a nucleotide sequence coding a natural-occurring protein without losing the proteins functions and properties. When the claimed invention is related to derivatives of a short sequence, however, it is very likely that the function would be lost through a modification of nucleotides.

(5) The claimed invention concerns any several contiguous amino acid fragments of a pathogenic viral antigen. (ex. A polypeptide in substantially isolated form comprising a contiguous sequence of at least 8 amino acids encoded by the genome of X virus and comprising an antigenic determinant, wherein X virus is characterized by 940 amino acid sequence in Fig. 1.)

What description meets the enablement requirement ?

The USPTO points that it depends on whether or not the entire polypeptide sequence is disclosed and what "biological activity" is claimed.

The JPO also explains that its distinctiveness is extremely important and such conditions as immunogenicity are required in addition to the above-mentioned conditions with regard to vaccines.

In contrast, the EPO states that this would fulfil the enablement requirement because such polypeptides could be obtained by a person skilled in the art.

(6) The claimed DNA is characterized by its identity with a certain nucleotide sequence. (ex. A DNA sequence having at least x% identity to a DNA sequence in Fig. 1)

Even if its rate is low (ex. $x=40\%$), does this claimed invention meet the enablement requirement ?

The USPTO states that there would be no problem "making" but there might be an issue as to "using" the sequence. The JPO states that the enablement requirement would not be met because such a claim clearly includes DNAs which do not satisfy the requirement for utility.

On the other hand, the EPO only replies that the enablement requirement would in principle be met.

(6') If the claimed DNA is characterized only by its identity with a certain nucleotide sequence, is the enablement requirement met or not ?

If the claimed DNA is characterized by its identity with a certain nucleotide sequence and is defined by its function, is the enablement requirement met even if the rate of identity is low ?

There are some differences among answers of the three Offices.

The USPTO replies that it depends on what the invention actually is, and comments that it is important to permit applicants to claim DNAs that may have only a limited amount of identity with a specific sequence. The USPTO explains that even such low identity DNAs could, for example, still code for the same protein as the specific sequence.

Because of the underlying factual determinations necessary to determine enablement, each application must be reviewed on its facts and few per se rules can be articulated.

The EPO replies that the enablement requirement would be met in the both cases.

On the other hand, the JPO states that in the both cases the enablement requirement would not be met.

(7) The claimed DNA is not characterized by its nucleotide sequence but only by its function. (ex. A DNA sequence encoding protein X)

Does this claimed invention meet the enablement requirement ?

The answers of the three Offices to this question are similar to the prior cases 1.1.1.1 (1), 1.1.1.2.1(1) and 1.1.1.2.2(1).

(8) The claimed DNA is characterized neither by its origin nor by its nucleotide sequence.

In the description of the invention, there is only one working example of cloning cDNA from a specific origin (ex. mouse).

Where the claim contains DNA prepared from any other origins (ex. human) than mouse, does this claimed invention meet the enablement requirement ?

The three Offices have the similar opinion; namely, "it would require an analysis of both the specification description and the state of the art at the time of filing" (the USPTO), "if a person skilled in the art could obtain the DNA from other origins without exerting inventive skill" (the EPO) and "taking into account the common general knowledge as of the filing" (the JPO).

**(9) The claimed invention is a monoclonal antibody to a novel protein.
(ex. A monoclonal antibody which specifically binds to protein X.)**

Where there is no working example of preparing a monoclonal antibody to the novel protein in the description of the invention, what description meets the enablement requirement ?

If the immunogenicity of the protein is recognized, does this claimed invention meet the enablement requirement ?

If so, can its immunogenicity be recognized with descriptions as follows ? :

- (a) The molecular weight of the novel protein is more than 10kDa.**
- (b) With regard to inventions for diagnostic use, the novel protein is not in human being originally.**
- (c) An antibody has already been prepared by an immunogenic protein closely similar to the above novel protein.**

(10) The claimed invention is a certain monoclonal antibody.

In the case where there is a working example of producing the monoclonal antibody in the description of the invention, but the hybridoma producing the monoclonal antibody is not deposited, what description meets the enablement requirement ?

There are some differences among answers of the three Offices.

The USPTO explains there is no general rule, and each application must be separately considered based on the disclosure provided and the particular antibody claimed.

On the other hand, the EPO suggests it is well-known that by use of the classical fusion technique of Kohler and Milstein, monoclonal antibodies against a predetermined antigen can be routinely obtained, i.e. without performing inventive skill; no problems as to the enablement requirement would appear to arise in cases (a) - (c) of the question (9). On this point, the JPO states about the immunogenicity that (a) and (b) themselves are insufficient and (c) is enough.

As to specific monoclonal antibodies, however, the three Offices answer the similar way that the deposition of cells is necessary in principle.